Some Observations on the Phenoltetrachlorphthalein Test as a Means of Determining Liver Function

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SOME OBSERVATIONS ON THE PHENOLTETRACHLOR-PHTHALEIN TEST AS A MEANS OF DETERMINING LIVER FUNCTION.*

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Since the publication of the work of Rowntree, Hurvitz and Bloomfield,[1] in 1913, advocating the use of phenoltetrachlorphthalein as a test for liver function, considerable attention has been directed to this test. Inasmuch as the dye was first collected through the feces, many discrepancies were noted as to its determination by various observers; so that Whipple,[2] McLester and Frazier[3] and Kahn and Johnston,[4] report unfavorably concerning it, while Sisson,[5] Chesney, Marshall, and Rowntree,[6] and Krumbhaar,[7] on the other hand, consider it of considerable value as a means of determining liver function.

On account of the great variations in result, McNeil[8] recommended the collection of the dye through the duodenal tube, and Aaron, Beck and Schneider,[9] as well as Piersol[10] have since advocated this method. Following the plan advised by Aaron and his co-workers, we have given 169 single injections of this dye to 93 individuals, utilizing the stable solution recommended by them.

Technic. The technic in carrying out the test, is as follows: Immediately before injecting the dye, the duodenal tube being held *in situ*, with a strip of adhesive wrapped around it beyond the third mark and the free end of the adhesive strapped on the cheeks, the patient is given two or three glasses of ice-cold water to drink. In nervous hypersensitive patients, hot water should be introduced very slowly through the duodenal tube. The object of the water is to stimulate the gall-bladder to contract, as well as to relax the sphincter of Oddi and to provide a free flow through the tube. When

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this flow is established, 1 cc containing 75 mgm. of the disodium salt of the phenoltetrachlorphthalein is diluted with 5 cc of sterile physiological salt solution and injected intravenously. It is better in our experience to detach the needle from the syringe and insert it first into the vein, as the color of the dye makes it difficult to note the return of the blood through the needle. A bit of gauze is held firmly around the needle when it is withdrawn to prevent any return leakage, as the phthalein is extremely irritating to the subcutaneous tissues.

Previous to utilizing this method of dilution, considerable irritation of the arm resulting from a leakage of the dye through the vein or the escape of even as small an amount as a drop into the subcutaneous tissues was produced and several instances of thrombosis resulted from the action of the concentrated dye on the walls of the vein at the site of the injection; but since using sterile salt as a diluent, we have not noted a single untoward effect.

The flow from the duodenal tube is allowed to run by gravity into successive porcelain basins, containing 2 cc of a 40 per cent sodium hydrate solution to secure the time of maximum appearance of the dye. If the flow through the tube ceases, the patient should be given more water and in some cases where there is no flow of bile, by the use of the water, 3 cc of a 10 per cent hydrochloric acid solution in 30 cc of water should be injected through the duodenal tube.

Due to the possibilities of error we have not followed the method advocated by Piersol;[10] that is, the estimation of the output of the dye, but have limited our studies to its time appearance, which according to our experience, has been extremely constant.

The usual cause of failure to obtain the dye in a normal individual is due either to not having the duodenal tube in proper position or to the absence of a free return flow of water through the tube.

The tables on pages 3, 4 and 5 illustrate the time of excretion of the dye in normal and pathological cases.

As a result of the study of our 93 cases the following observations are noted.

Method of Administration. The dye should only be utilized intravenously; when given subcutaneously once and intramuscularly twice to a normal individual having an excretion time of fifteen minutes, there was no appearance in two hours when the tube was withdrawn. Preceding the administration of the dye by a non-surgical biliary drainage, has apparently no effect on the time of excretion.

Daily Variation in Normal Individuals. A reference to the table in which the test was made in 20 normal individuals (in every instance more than once) reveals variations of only a few minutes from day to day in the time of appearance of the dye. A longer variation than this we consider indicates either imperfect technic or some pathological affection.

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
1	1	B.	2- 4-22	21	M.	Achylia gastrica	7 min.	9	Constant.
	2		1-31-22				8	12	
2	3	S.	3-15-22	25	M.	Catarrhal jaundice (subsiding)	8	30	
	4		3-17-22				14	30	Faint.
3	5	S.	3-21-22	38	M.	Chronic cholecystitis	8	14	
	6		5-18-22				12	15	
4	7	F.	3-22-22	55	F.	Paresis (early)	8	11	
5	8	C.	2-20-22	26	..	Typhoid relapse	9	11	
6	9	B.	12-22-21	45	M.	Cholelithiasis, chronic cholecystitis	None in	60 min.	
	10		12-23-21				None in	75 min.	
	11		12-24-21				None in	90 min.	
	12		12-28-21				18	24	
	13		1- 5-22				8	12	
7	14	A.	1-25-22	40	M.	Neurosis	20	25	
	15		2- 3-22				9	15	
8	16	C.	3-23-22	35	M.	Gastric neurosis	9	14	
9	17	G.	1-29-22	65	F.	Chronic cholecystitis, cholangitis and gall-bladder calculi	9 min.	13 min.	
	18		2-15-22				15	16	
10	19	D.	5-10-22	55	F.	Chronic cholecystitis, adhesions and morphinism	10	14	
11	20	D.	4-24-22	15	M.	Acute catarrhal jaundice	10	14	
	21		4-26-22				10	16	
12	22	H.	3- 8-22	28	M.	Psychoneurosis	10	12	
	23		3-10-22				10	16	
13	24	Q.	3- 6-22	58	M.	Psychoneurosis	10	10	
14	25	P.	5- 7-22	38	M.	Malnutrition, visceroptosis, neurosis	10	14	
15	26	S.	4-25-22	55	M.	Arteriosclerosis and myocardial insufficiency	10	15	
16	27	T.	.....	14	M.	Epilepsy, achylia nervosa	11	14	
17	28	K.	3-29-22	35	M.	Cancer of rectum with abdominal metastases	12		Faint.
18	29	H.	5- 5-22	55	M.	Chronic cholecystitis, gastric neurosis	10	14	
	30		5- 7-22				15	6	
	31		5- 9-22				10	14	
	32		5-15-22				15	45	
	33		5-16-22				15	18	
	34		5-20-22				19	22	
	35		5-22-22						
	36		5-31-22				20	25	
	37		5-24-22			Given adrenalin ℳx	18		
	38		1-11-22	40	M.	Syphilis, secondary	16	18	
19	39	G.	1-15-22				10	14	
20	40	B.	3- 3-22	..	..	Posteclampsia	11 min.	15	
21	41	T.	1-11-22	42	M.	Chronic cholecystitis, eczema	14	20	
	42		1-17-22				13	13	Faint.
	43		1-14-22				12		
22	44	C.	4-12-22	30	M.	Acute cholecystitis	12	18	
23	45	B.	3-27-22	60	F.	Syphilis of liver	11	12	
	46		5- 8-22				25		
24	47	A.	2- 9-22	35	M.	Cardiac decompensation (Chronic passive congestion. Autopsy)	13	16	
25	48	A.	1-13-22	45	M.	(After operation for stones)	15	18	
	49		1-16-22			Gall-bladder draining	12	16	
	50		1-23-22				11	14	
26	51	P.	1-12-22	45	F.	Chronic polyarthritis	20		
	52		1-16-22				13		
	53		1-18-22				13		
27	54	A.	1-27-22	48	F.	Neurosis	14	30	
	55						13	23	
28	56	W.	2- 6-22	45	M.	Gout	13	26	

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
29	57	W.	12–24–21	25	M.	Addison's disease	20	22	
	58		12–27–21				12	14	
	59		1–11–22				10	16	
30	60	R.	1–18–22	26	F.	Pregnancy (8 mos.)	13	15	
31	61	W.	2–10–22	30	F.	Posteclampsia	13	16	
32	62	S.	1–12–22	40	F.	Cholecystitis	12		
	63						20		
	64						12		
	65						20?		
	66						21		
33	67	C.	5– 9–22	30	M.	Epilepsy, polycythemia	12	14	
34	68	A.	3– 9–22	25	M.	Bichloride poisoning	15	17	
35	69	B.	1–26–22	48	M.	Cancer stomach (inoperable)	15	18	
36	70	K.	3–24–22	40	M.	Normal	14	16	
	71		3–28–22				19	19	
37	72	L.	1–18–22	32	F.	Pregnancy (8 months)	14	18	
38	73	H.	3–19–22	42	F.	Cholelithiasis	15	25	
	74						14	25	
39	75	M.	4– 3–22	24	F.	Subacute cholecystitis	15	16	
40	76	M.	3– 3–22	50	..	Cholecystitis and cholelithiasis	15	18	
41	77	P.	2–18–22	50	F.	Eclampsia (3 days after delivery)	15	16	
42	78	T.	3–30–22	38	F.	Hyperacidity, cholecystitis	15	18	
43	79	T.	3– 4–22	38	F.	Chronic cholecystitis	16	18	
44	80	M.	3– 1–22	40	F.	Aortic aneurysm	18	35	Faint.
45	81	J.	1–20–22	55	M.	Chronic alcoholism	17	19	
	82		1–21–22				14	16	
	83		1–24–22				15	17	
46	84	C.	1–17–22	29	M.	Diabetes (severe)	16	19	
47	85	B.	4– 6–22	65	F.	Cancer pancreas and liver (non-obstructive)	16	45	
48	86	F.	3– 1–22	40	F.	Visceroptosis	18	20	
49	87	B.	1–17–22	22	M.	Syphilis (secondary)	17	19	
	88						19	22	
50	89	S.	1–17–22	18	M.	Rupture of liver	19	21	
51	90	A.	1–17–22	32	M.	Thyrotoxicosis	12	16	
	91		1–19–22				22		
52	92	S.	1–14–22	45	M.	Appendicitis	19	22	
53	93	B.	2– 6–22	36	M.	Typhoid (convalescing)	21		
	94		2– 8–22			Acute cholecystitis	14		
	95		2–20–22				15	30	
	96		2–23–22				20	20	
54	97	S.	12–23–21				20	22	
55	98	S.	12–24–21	58	M.	Malnutrition	20	22	
56	99	W.	3–23–22	70	M.	Chronic cholecystitis with cholelithiasis	10	22	Intermittent.
	100		3–17–22				14	25	
	101		3–21–22				15	16	Faint.
	102		3–27–22				12	16	
57	103	Y.	3–12–22	26	F.	Chronic cholecystitis, neurosis	20	20	Faint.
58	104	C.	1–10–22	11	F.	Epilepsy, hyperpituitarism	21		
59	105	A.	1– 5–22	65	M.	Pancreatitis, cholecystitis, cholelithiasis	21	25	
	106						20	26	
	107						22	27	
60	108	B.	2–16–22	70	M.	Chronic cholecystitis	22	22	Faint after 22 min.
61	109	H.	2– 8–22	45	M.	Chronic cholecystitis	22	26	
62	110	H.	.....	62	M.	Chronic cholecystitis, cholelithiasis	23	33	
	111		3–25–22				23	33	
63	112	S.	2–10–22	55	M.	Diabetes (moderate)	25	25	Faint.
64	113	W.	2–24–22	3	M.	Hepatitis	0 in ½ hr. (subcutaneously).		
65	114	C.	5– 1–22	55	M.	Cirrhosis of liver (fatal)	0 in 120 min.		
	115						0 in 60 min.		
66	116	W.	3–21–22	45	F.	Chronic pancreatitis, hydrops of gall-bladder	0 in 120 min.		
	117		3–19–22				0 in 60 min.		

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
	118		4–12–22				0 in 50	min.	
	119		2– 4–22				0 in 24	0 min.	
	120		2–20–22				0 in 75	min.	
	121		2–24–22				Faint in	120 min.	
	122		2–17–22				0 in 75	min.	
67	123	W.	12–23–22	58	M.	Chronic pancreatitis	45	45	
68	124	S.	2– 1–22	25	F.	Eclampsia (1st test while in	0 in 40	min.	
	125					eclampsia, just after con-	0 in 18	0 min.	
	126					vulsion; last test after re-	195 faint		
	127					covery)	18		
69	128	T.	1–10–22	70	F.	Cancer head pancreas with obstruction	0 in 2	hrs.	
70	129	S.	1–11–22	50	F.	Cancer head pancreas, cholecystgastrostomy	0 in 2	hrs.	
71	130	W.	2–13–22	3	M.	Cirrhosis of liver	0 in 12	0 min.	
	131		2–21–22				0 in 45	min.	
	132		3 –2–22				20 very	faint 90	until 45 min.
72	133	S.	2 –7–22	38	F.	Cholelithiasis, acute cholecystitis	21	24	
	134		2–20–22				18	22	
	135		2–22–22				24 faint	24	
	136		2–27–22				18		
	137		2–14–22				21	24	
	138		3– 2–22				18	20	
73	139	G.	1–11–22	45	M.	Cancer stomach	21	28	
74	140	L.	5–13–22	74	F.	Stone in common duct	0 in 40	min.	
	141		5–15–22			Starvation (4 to 8 days)	0 in 40	min.	
	142		5–16–22				19	35	Faint.
	143		5–17–22				17	20	Intermittent.
75	144	B.	2–25–22	45	F.	Stone in common duct, jaundice	19	29	
	145		3– 8–22						
	146		3–20–22				40		
	147		3–21–22				14	47	Intermittent.
76	148	B.	1–21–22	73	M.	Stone in common duct, cholangitis (severe)	19	19	Very faint.
	149		1–22–22				35	78	Very faint.
	150		1–23–22				60	60	Very faint.
77	151	B.	2–13–22	46	F.	Cholelithiasis, cholecystitis, syphilis of liver	25 single	spurt at	25, none after.
	152		5–18–22				70 faint,	intermittent	pale bile.
78	153	G.	4– 6–22	55	..	Stone in common duct	36	36	Faint, intermittent.
79	154	M.	4–20–22	44	F.	Stone in common duct	40		
80	155	S.	3–13–22	30	M.	Cirrhosis of liver, syphilis	45 faint	120 normal.	
81	156	B.	4– 1–22	52	M.	Cancer head pancreas (obstructive)	0 in 3	hrs.	
82	157	T.	4–13–22	30	M.	Salvarsan jaundice	0 in 75	minutes	bile flows freely.
83	158	B.	4–21–22	58	M.	Cancer pancreas	0 in 3	hrs.	
84	159	B.	6– 2–22	18	F.	Pregnancy, cholelithiasis	18	34	
85	160	C.	5–29–22	40	F.	Intestinal toxemia	45 faint		
	161		5–26–22			Adrenalin ℳ V (h)			
86	162	S.	5–30–22	35	M.	Dysentery	20	25	
87	163	R.	5–22–22	50	M.	Cholelithiasis	16	28	
88	164	W	5–23–22	21	M.	Neurosis	15	20	
89	165	G.	5–20–22	26	F.	Peptic ulcer	20	20	Intense.
90	166	J.	6– 5–22	40	M.	Chronic cholecystitis	13	35	Intermittent.
91	167	G.	6– 6–22	30	M.	Biliary stasis	10	25	Intermittent.
92	168	H.	6– 6–22	30	M.	Biliary stasis	10	55	Intermittent.
93	169	Dr. B.	6– 6–22	50	M.	Atrophic cirrhosis	0 in 3	hrs.	

Effect of Starvation. Following a six-day or an eight-day fast in the same patient, the time of excretion was nineteen and seventeen minutes, respectively, indicating that starvation has but little direct influence upon the appearance of the dye.

Age. The variations of age of the individuals in our table ranged from thirty-seven months to seventy-two years, but both of these extremes were in pathological cases. The average of the normals reveals practically no variation according to age.

The average rate of excretion of all normal cases is thirteen and eight-tenths minutes.

Sex. In 56 males, the average time of excretion was thirteen and seven-tenths minutes; and in 37 females, thirteen and nine-tenths minutes. There is therefore no difference attributable to sex. Aaron reports an average of seventeen and two-tenths minutes in 10 normal individuals, utilizing the same quantity of dye, while Piersol's results, using double the quantity in 15 normal individuals, were lower than ours by several minutes.

Pregnancy. Uncomplicated pregnancy in 8 instances showed an average excretion of fourteen minutes, *viz.*, somewhat below the average normal.

Diabetes. There were 2 instances with an average excretion time of twenty-five minutes and sixteen minutes, averaging nineteen and a half minutes. There appeared to be no relation as to the severity of the disease to the rate of excretion of the dye.

Epilepsy. In 3 cases of epilepsy the readings were twenty-one minutes; twelve minutes and eleven minutes. The average was fourteen and nine-tenths minutes.

Psychoneurosis. The average excretion of 9 cases was twelve and eight-tenth minutes.

Toxemias. Three cases of eclampsia examined immediately after the convulsive stage, average fifteen minutes. A fourth case was done during the stage of convulsions and repeated 4 times as the patient improved. In this case the results were parallel with the condition of the patient. At first there was no excretion in forty minutes; when the patient had a convulsive seizure and removed the tube; at the second trial there was no excretion in one hundred and eighty minutes; in the third, there was just a trace one hundred and ninety-five minutes and in the last, when the patient's symptoms had cleared up, the time of excretion was normal, namely eighteen minutes. In a case of bichloride poisoning, three days after the patient had taken 12 gr. there was no delay in the initial appearance of the phthalein; the patient, however, had but the mildest symptoms at the time of the examination.

Malnutrition. The average appearance in 2 instances was fifteen minutes.

Catarrhal Jaundice. In 2 subsiding cases the average was ten and a half minutes.

Endocrine Disturbances. A case of Addison's disease averaged fourteen minutes for 3 tests; 1 of hyperpitutarism with epilepsy was twenty-four minutes; 1 of thyrotoxicosis averaged seventeen minutes.

Syphilis. In 2 cases of secondary syphilis, the average secretion was noted in sixteen minutes in 4 examinations. Several cases of syphilis with complications are summarized in the accompanying table.

Acute Infections. Five tests in 2 typhoid fever patients averaged fifteen and eight-tenths minutes.

Cholecystitis with Cholelithiasis. The rate of excretion in 40 cases of cholecystitis averaged seventeen minutes.

Stone in the Common Duct with Jaundice. The average rate of excretion was twenty-eight minutes in 9 cases. In 5 others there was no excretion whatever of the dye during the entire period of examination.

Cancer of the Liver. In a case which came to autopsy two days following the test, the time of excretion was twenty-five minutes; in another instance it was forty-five minutes.

Atrophic Cirrhosis of the Liver. In 2 instances of this affection, there was no excretion in two hours or in forty-five minutes respectively, when the tube was removed.

Cancer of the Pancreas. In 1 case there was no excretion in 3 tests in two hours; in the second, the average rate was forty-five minutes.

Jaundice Following the Use of Arsphenamine. In one instance there was no excretion in seventy-five minutes.

Cardiac Disease. In a single case of myocarditis the rate of excretion was eighteen minutes; in 1 of chronic passive congestion, two weeks before death, it was thirteen minutes.

Conclusions. From the examinations made by us, as well as those by Aaron and others, regarding the phenoltetrachlorphthalein test for liver function, we believe the following conclusions may safely be drawn.

1. The phenoltetrachlorphthalein test is a valuable means of determining liver function.

2. In order to obtain reliable results the technic in performing the test must be carefully carried out in every detail. On this account the preparation utilized must be stable and free from all deterioration.* The tube must be *in situ* and the drip well established. Under these conditions, the end-result is definite and distinct and there is little or no difficulty in noting the maximum appearance of the dye.

3. In normal individuals the appearance of the excretion as measured day by day is extremely constant; the average being, according to our experience, in thirteen and seven-tenths minutes. A delay of more than twenty-three minutes in the excretion of the dye indicates the presence of some hepatic disease or mechanical obstruction at some point between the biliary ducts and the ampulla of Vater. The most marked delay occurred in biliary cirrhosis; in obstruction the delay varied from day to day when the obstruction was due to stone.

* The phenoltetrachlorphthalein ampules in stable form used in the performance of these tests were furnished us by Messrs. Hynson, Westcott and Dunning, of Baltimore, to whom we desire to acknowledge our thanks and from whom this preparation can now be obtained.

4. The test has proved useful as a means of checking up the technic of non-surgical biliary drainage. It is also of value in the diagnosis of cirrhosis and carcinoma of the liver and obstruction of the common duct from stone or tumor.

The manner in which the tetrachlorphthalein flows may aid in differentiating cases in which there is delay, especially between cholelithiasis, cancer and cirrhosis of the liver and external causes of obstruction. The flow in cases of calculus is usually intermittent and presents a greater variation from day to day, whereas in cirrhosis and other forms of obstruction, the flow after once beginning is constant and there is but an extremely slight daily variation.

5. Finally from these observations it is evident that the tetrachlorphthalein test is of considerable value as a means of determining liver function, and when properly performed may be of great aid in diagnosis.

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